PACKAGE LEAFLET

Package leaflet: Information for the patient

Leflunomide 10 mg Film-coated Tablets
Leflunomide 20 mg Film-coated Tablets

(leflunomide)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Leflunomide is and what it is used for

Leflunomide belongs to a group of medicines called anti-rheumatic medicines. Leflunomide is used to treat adult patients with active rheumatoid arthritis.

Symptoms of rheumatoid arthritis include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (reduction of red blood cells).

2. W hat you need to know before you take Leflunomide

Do not take Leflunomide
- if you are allergic to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome), to a medicine called teriflunomide (which is related to leflunomide) or to any of the other ingredients of this medicine (listed in section 6)
- if you have any **liver problems**,
- if you have moderate to severe **kidney problems**,
- if you have severely low levels of **proteins in your blood** (hypoproteinaemia),
- if you suffer from any problem which affects your **immune system** (e.g. AIDS),
- if you have any problem with your **bone marrow,** or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets due to causes other than rheumatoid arthritis,

- if you are suffering from a **serious infection**,
- if you are **pregnant,** think you may be pregnant or are breast-feeding
- if you are woman of child bearing age and not using effective contraception.

Warnings and precautions
Talk to your doctor or pharmacist before taking leflunomide:
- if you have ever suffered interstitial lung disease
- if you have ever had tuberculosis or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis.
- if you are **male** and wish to father a child. As it cannot be excluded that leflunomide passes into semen, reliable contraception should be used during treatment with leflunomide. Men wishing to father a child should contact their doctor who may advise you to stop taking Leflunomide and take certain medicines to remove leflunomide rapidly and sufficiently from your body. You will then need a blood test to make sure that leflunomide has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.
- if you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.
- if you will have or have had recent major surgery, or if you still have an unhealed wound following surgery. Leflunomide may impair wound healing.

Leflunomide can occasionally cause some problems with your blood, liver, lungs or nerves in your arms or legs. It may also cause some serious allergic reactions (including Drug Reaction and Eosinophilia and Systemic Symptoms [DRESS]), or increase the chance of a severe infection. For more information on these, please read section 4 'Possible side effects'.

DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

Your doctor will carry out **blood tests** at regular intervals, before and during treatment with Leflunomide, to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as Leflunomide can cause an increase in blood pressure.

Tell your doctor if you have unexplained, persistent diarrhoea. Your doctor may perform additional tests to establish its cause.

Tell your doctor if you develop skin ulcer during treatment with Leflunomide (see also section 4).

Children and adolescents
Leflunomide is not recommended for use in children and adolescents below 18 years of age.

Other medicines and Leflunomide
Tell your doctor or pharmacist if you are taking, have recently taken or might any other medicines.

This is especially important if you are taking:
- other medicines for **rheumatoid arthritis** such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine, Tumour

Necrosis Factor alpha-Inhibitors (e.g. adalimumab, infliximab) and other immunosuppressive drugs (e.g. methotrexate) as these combinations are not advisable,

- **a medicine called colestyramine (used to reduce high cholesterol) or activated charcoal** as these medicines can reduce the amount of Leflunomide which is absorbed by the body

- a medicine called teriflunomide (used for the treatment of multiple sclerosis)
- warfarin and other oral medicines used to thin the blood, as monitoring is necessary to reduce the risk of side effects of this medicine
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhoea
- theophylline for asthma
- tizanidine, a muscle relaxant
- oral contraceptives (e.g. ethinylestradiol and levonorgestrel)
- rifampicin (used in the treatment of tuberculosis)

- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indometacin, ketoprofen for pain or inflammation
- furosemide for heart disease (diuretic, water pill)
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- cimetidine (for excess stomach acid).

If you are already taking a non-steroidal **anti-inflammatory** drug (NSAID) and/or **corticosteroids**, you may continue to take them after starting Leflunomide.

Vaccinations
If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking leflunomide, and for a certain amount of time after stopping treatment.

Taking Leflunomide with food, drink and alcohol
Leflunomide may be taken with or without food.
It is not recommended to drink alcohol during treatment with Leflunomide. Drinking alcohol while taking Leflunomide may increase the chance of liver damage.

Pregnancy and breast-feeding
Do not take Leflunomide if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking leflunomide, the risk of having a baby with serious birth defects is increased. Women of childbearing potential must not take Leflunomide without using reliable contraceptives measures.

Tell your doctor if you plan to become pregnant after stopping treatment with Leflunomide, as you need to ensure that all traces of leflunomide have left your body before trying to become pregnant. This may take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of leflunomide from your body.

In either case it should be confirmed by a blood test that leflunomide has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking leflunomide or in the two years after you have stopped treatment, you must contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove Leflunomide rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Breast-feeding
Do not take Leflunomide when you are **breast-feeding**, as leflunomide passes into the breast milk.

Driving and using machines
Leflunomide can make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive, or use machines.

Leflunomide contains **lactose**.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Leflunomide

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose of Leflunomide is 100 mg once daily for the first three days.
After this, most patients need a dose of:
- For rheumatoid arthritis: 10 or 20 mg Leflunomide once daily, depending on the severity of the disease.

Swallow the tablet **whole** and with plenty of **water**. Leflunomide can be taken with or without food.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.
You will normally take Leflunomide over long periods of time.

If you take more Leflunomide than you should
If you take more Leflunomide than you should, contact your doctor or get other medical advice.
If possible, take your tablets or the box with you to show the doctor.

You may have any of these symptoms: stomach pain, diarrhoea, itching and rash.

If you forget to take Leflunomide
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** and stop taking Leflunomide:
- if you experience **weakness**, feel light-headed or dizzy or have **difficulty breathing,** (with or without skin rash including red itchy skin, swelling of the hands, feet ankles, face, lips, mouth or throat with difficultly in swallowing), as these may be signs of a serious allergic reaction,
- if you develop a **skin rash** or **inflammation and ulcers in your mouth**, as these may indicate severe, sometimes life-threatening allergic reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS) see section 2.

Tell your doctor **immediately** if you experience:
- **pale skin**, **tiredness,** or **bruising,** as these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood,
- **tiredness**, **abdominal pain**, or **jaundice** (yellow discolouration of the eyes or skin), as these may indicate serious conditions such as liver inflammation (hepatitis) or failure, which may be fatal,
- any symptoms of an **infection** such as **fever, ulcers in your mouth (signs of agranulocytosis-marked decrease of some white blood cells-very rare), sore throat** or **cough,** as this medicine may increase the chance of a severe infection, including sepsis(rare), which may be life- threatening,
- inflammation of blood vessels (vasculitis, including cutaneous necrotising vasculitis),
- **cough** or **breathing problems** as these may indicate problems of the lung (interstitial lung disease or pulmonary hypertension),
- unusual tingling, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy)
- loss of appetite; tummy pain; tenderness over your abdomen when it's touched; feeling sick and generally unwell, vomiting, fever, these may be signs of inflammation of the pancreas (pancreatitis),
- severe pain or ache on one or both sides of your back, sudden spasms of excruciating pain – this usually starts in the back below your ribs, radiating around your abdomen, and sometimes to your groin and genitals; blood in your urine; feeling sick or vomiting; needing to urinate often, or feeling a burning sensation during urination; fever; nausea, vomiting; rash; weight gain; these may be signs of kidney failure,
- cutaneous lupus (characterised by rash/erythema on skin areas that are exposed to light).
- colitis (causing unexplained, persistent diarrhoea)

Other side effects:

Common (may affect up to 1 in 10 people):
- mild allergic reactions,
- loss of appetite, weight loss (usually insignificant),
- tiredness (asthenia),
- headache, dizziness,
- abnormal skin sensations like tingling (paraesthesia),
- mild increase in blood pressure,
- diarrhoea,
- nausea, vomiting,
- abdominal pain,
- an increase in some liver test results,
- increased hair loss,
- eczema, dry skin, rash, itching,

- tendonitis (pain caused by inflammation in the membrane surrounding the tendons usually in the feet or hands),
- an increase of certain enzymes in the blood (creatine phosphokinase).

Uncommon (may affect up to 1 in 100 people):
- a decrease in the levels of potassium in the blood,
- anxiety,
- taste disturbances,
- urticaria (nettle rash),
- tendon rupture,
- an increase in the levels of fat in the blood (cholesterol and triglycerides),
- a decrease in the levels of phosphate in the blood.

Rare (may affect up to 1 in 1000 people):
- an increase in the numbers of blood cells called eosinophiles (eosinophilia);
- severe increase in blood pressure,

- an increase of certain enzymes in the blood (lactate dehydrogenase).

Not known (frequency cannot be estimated from the available data)
Other side effects such as, a decrease in the levels of uric acid in your blood, pulmonary hypertension male infertility (which is reversible once treatment with this medicine is stopped) and psoriasis (new or worsening), skin ulcer (round, open sore in the skin through which the underlying tissues can be seen) may also occur.

Medicines like leflunomide have been associated with an increased risk of developing cancers.

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Leflunomide

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister / bottle and carton. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Leflunomide contains

- The active substance is leflunomide. One film-coated tablet contains 10 or 20 mg of leflunomide.

The tablet core: contains microcrystalline cellulose, pregelatinised maize starch, povidine K 30 (E1201), crospovidone (E1202), silica colloidal anhydrous, magnesium stearate (E470b) and lactose monohydrate.

The film coating additionally contains titanium dioxide (E171), hypromellose (E464) and macrogol. The 20 mg tablet also contains talcum and yellow iron oxide (E172).

What Leflunomide looks like and contents of the pack

- Leflunomide 10mg film-coated tablets are white, round biconvex tablets with a diameter of about 6.1mm. The product is packaged in a cardboard box containing blisters or bottle with an integrated desiccant (white silica gel) or desiccant sachet. Do not eat the desiccant.
  Pack sizes of 30, 100 film-coated tablets.

- Leflunomide 20mg film-coated tablets are yellow, round biconvex, with a score line on one side with a diameter of about 8.1mm. The product is packaged in a cardboard box containing blisters or a bottle with an integrated desiccant (white silica gel) or desiccant sachet. Do not eat the desiccant.
  Pack sizes of 30, 100 and 500 (only in HDPE bottle) film-coated tablets are available.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Mylan, Potters Bar, Hertfordshire EN6 1TL United Kingdom

Manufacturer

Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13 Ireland

Pharmathen S.A., Dervenakion 6, 15351 Pallini Attiki, Greece

Pharmathen International S.A. Industrial Park Sapes, Rodopi Prefecture, Block No 5, Rodopi 69300, Greece

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